

Endocrine drugs





Drugs affecting the endocrine system

- Drugs Affecting Pituitary and Thyroid
- Drugs for Diabetes
- Estrogens Progestins and Androgens
- Adrenal Hormones
- Drugs affecting bone metabolism



Hormone pharmacotherapy

- Hormones are used as:
 - Replacement therapy
 - Antineoplastics
 - Natural therapeutic effects
 - Exaggerated response or suppression of body defenses
- Hormone blockers are used to inhibit actions of certain hormones



Drugs affecting the pituitary and thyroid



Introduction

- The neuroendocrine system, controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues
- The endocrine system releases hormones into the bloodstream, which carries these chemical messengers to target cells throughout the body
- Hormones have a longer response time than nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months



Introduction

- The nervous system and the endocrine system are closely interrelated
- The release of hormones could be stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses



Hypothalamus and anterior pituitary hormones

- The hormones secreted by the hypothalamus and the pituitary are all peptides or low-molecular-weight proteins that act by binding to specific receptor sites on their target tissues
- The hormones of the anterior pituitary are regulated by neuropeptides that are called either “releasing” or “inhibiting” factors or hormones produced in the hypothalamus



Hypothalamus and anterior pituitary hormones

- The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors
- The protein precursors then undergo post-translational modification to produce hormones released into the circulation



Hypothalamus and anterior pituitary hormones

- Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary
- The hypothalamic-releasing hormones are primarily used for diagnostic purposes (to determine pituitary insufficiency)
- The hypothalamus also synthesizes the precursor proteins of vasopressin and oxytocin, which are stored in the posterior pituitary



Hypothalamus and anterior pituitary hormones

- Some pituitary hormone preparations are used therapeutically for specific hormonal deficiencies but most have limited therapeutic applications
- Hormones of the anterior and posterior pituitary are administered either IM, SC, or intranasally but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes in GIT



Hypothalamus and anterior pituitary hormones

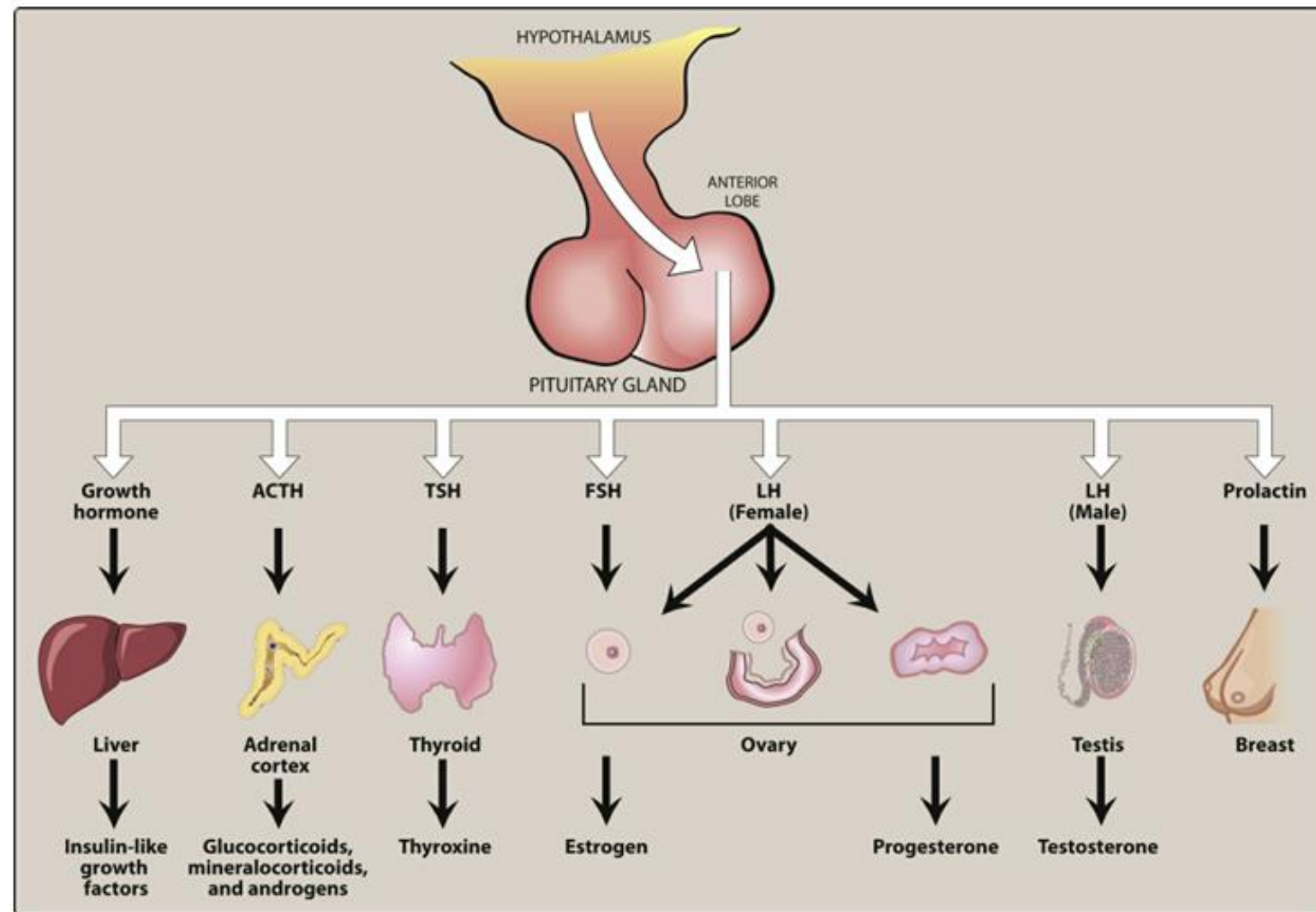


Figure 23.2 Anterior pituitary



Hypothalamus and anterior pituitary hormones

TABLE 37–1

Links between hypothalamic, anterior pituitary, and target organ hormone or mediator.¹

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+), Somatostatin (–)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+) ²	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (–)	Breast	—

¹ All of these hormones act through G protein-coupled receptors except GH and PRL, which act through JAK/STAT receptors.

² Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (–), inhibitor.



Hypothalamus and anterior pituitary hormones

TABLE 46–1

HORMONES THAT INTEGRATE THE HYPOTHALAMIC-PITUITARY-ENDOCRINE AXIS

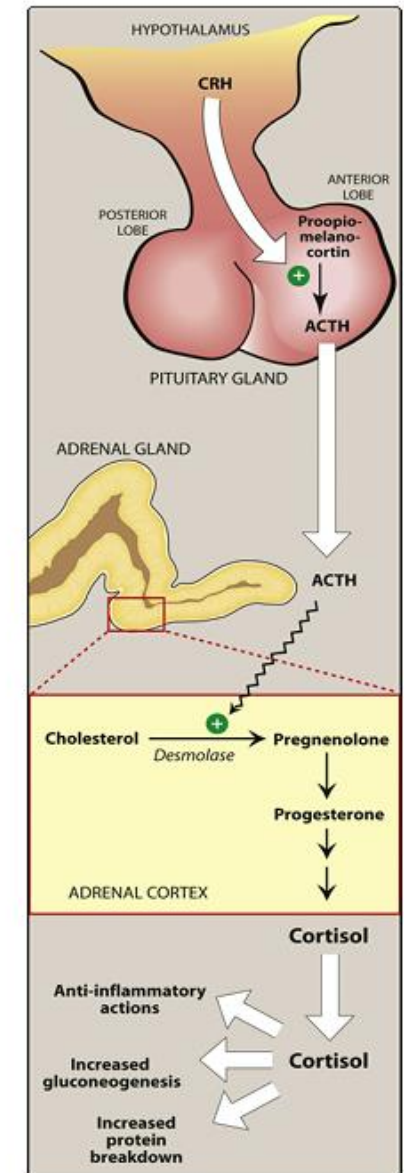
HYPOTHALAMIC HORMONE	EFFECT ON PITUITARY TROPHIC (SIGNAL) HORMONE	TARGET HORMONE(S)
Growth hormone–releasing hormone	↑↑ Growth hormone	IGF-1
Somatostatin	↓ Growth hormone ↓ Thyroid-stimulating hormone	
Dopamine	↓ Prolactin	—
Corticotropin-releasing hormone	↑ Corticotropin	Cortisol
Thyrotropin-releasing hormone	↑ Thyroid-stimulating hormone ↑ Prolactin	Thyroid hormone
Gonadotropin-releasing hormone	↑ Follicle-stimulating hormone ↑ Luteinizing hormone	Estrogen (f) Progesterone/estrogen (f) Testosterone (m)

f, female; m, male; ↑, increased production; ↓, decreased production.



Adrenocorticotrophic hormone (corticotropin)

- Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide pro-opiomelanocortin by the pituitary
- Adrenocorticotrophic hormone (ACTH), or corticotropin is a product of the posttranslational processing of this precursor polypeptide





Adrenocorticotrophic hormone (corticotropin)

- CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells
- ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM and the lowest in the late evening
- Stress stimulates ACTH secretion, whereas cortisol acting via negative feedback suppresses its release



Adrenocorticotrophic hormone (corticotropin)

Mechanism of action:

- The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces
- The occupied receptors activate G protein-coupled processes to increase cAMP, which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone)
- This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens



Adrenocorticotrophic hormone (corticotropin)

Therapeutic uses:

- Diagnostic use for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary)
- ACTH is used in the treatment of multiple sclerosis and infantile spasm (West syndrome)



Adrenocorticotrophic hormone (corticotropin)

Adverse effects:

- Similar to those of glucocorticoids
- Osteoporosis
- Hypertension
- Peripheral edema
- Hypokalemia
- Emotional disturbances
- Increased risk of infection



Growth hormone (somatotropin)

- A large polypeptide released by the anterior pituitary in response to growth hormone (GH)-releasing hormone produced by the hypothalamus
- Secretion of GH is inhibited by another pituitary hormone, somatostatin
- GH is released in a pulsatile manner, with the highest levels occurring during sleep
- With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass



Growth hormone (somatotropin)

- Somatotropin influences a wide variety of biochemical processes:
 - Stimulation of protein synthetic processes, cell proliferation and bone growth
 - Increased formation of hydroxyproline from proline boosting cartilage synthesis
 - Stimulates lipolysis
 - Antagonize insulin so as to elevate blood sugar level



Growth hormone (somatotropin)

- Synthetic human GH is produced using recombinant DNA technology and is called somatropin
- Mechanism of action:
 - Physiologic effects of GH are exerted directly at its targets
 - Others are mediated through the somatomedins— insulin-like growth factors I and II (IGF-I and IGF-II)

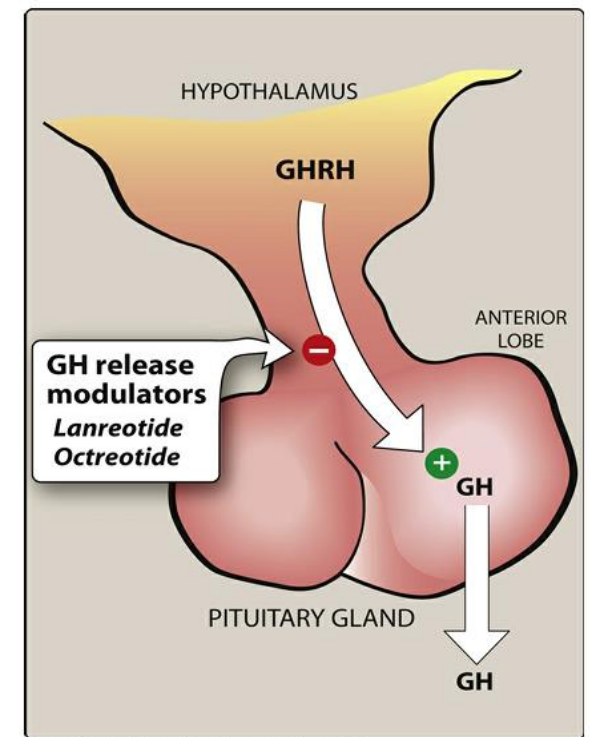


Figure 23.4 Secretion of growth hormone (GH). GHRH = growth hormone-releasing hormone.



Growth hormone (somatotropin) uses

- Somatotropin is used in the treatment of:
 - GH deficiency
 - Growth failure in children
 - Treatment of HIV patients with cachexia
 - GH replacement in adults with confirmed deficiency
- Somatotropin is administered by SC or IM injection.
- Although the half-life of GH is short, it induces release of IGF-1 from the liver, which is responsible for subsequent GH-like actions



Somatostatin

- Somatostatin: Growth hormone–inhibiting hormone
- In the pituitary somatostatin binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release
- Actions:
 - Inhibits the release of GH, insulin, glucagon, and gastrin



Octreotide

- A synthetic analog of somatostatin with a longer half-life
- The injectable solution and the depot formulation suppress GH and IGF-I for 12 hours and 6 weeks respectively
- Uses
 - Treatment of acromegaly caused by hormone-secreting tumors
 - Secretory diarrhea associated with tumors producing vasoactive intestinal peptide (VIPomas)



Octreotide

- Adverse effects:
 - Abdominal pain, flatulence, nausea, and steatorrhea
 - Delayed gallbladder emptying and asymptomatic cholesterol gallstones with long-term treatment



Lanreotide and Pasireotide

- Lanreotide
- Long-acting SST analogue that causes prolonged suppression of GH secretion every 4 weeks. Its efficacy appears comparable to that of the long-acting formulation of octreotide.
- Pasireotide
- Pasireotide is a long-acting SST analogue that is approved for the treatment of Cushing disease in patients who are ineligible for pituitary surgery or in whom surgery has failed.
- It is also approved for treatment of acromegaly.



Pegvisomant

- An analog of human GH with polyethylene glycol polymers attached
- Used for treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention
- Mechanism of action: an antagonist at the GH receptor that normalizes IGF-I levels



Gonadotropin releasing hormone (GnRH)

- Obtained from the hypothalamus
- Pulsatile secretion of GnRH is essential for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary
- Continuous administration inhibits gonadotropin release



GnRH analogs

- Leuprolide
 - Goserelin
 - Nafarelin
-
- GnRH synthetic analogs act as agonists at GnRH receptors
 - Effective in suppressing production of the gonadal hormones when administered continuously
 - Effective in the treatment of prostatic cancer, endometriosis, and precocious puberty



GnRH analogs: A/Es and contraindications

- In women, the analogs may cause hot flushes, sweating, diminished libido, depression, and ovarian cysts
- Contraindicated in pregnancy and breast-feeding
- In men
 - Initially cause a rise in testosterone that can result in bone pain
 - Hot flushes, edema, gynecomastia, and diminished libido



Gonadotropins

- Menotropins (human menopausal gonadotropins, or hMG) are obtained from the urine of postmenopausal women and contain FSH and LH
- Chorionic gonadotropin (hCG) is a placental hormone structurally related to LH which is an LH receptor agonist
- Urofollitropin: FSH obtained from postmenopausal women and is devoid of LH
- Follitropin alpha and follitropin beta are human FSH products manufactured using recombinant DNA technology



Gonadotropins

- Menotropins
- hCG
- Urofollitropin
- Follitropin alpha and follitropin beta
- All of these hormones are injected IM or SC
- Injection of hMG or FSH over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of hCG, ovulation occurs
- In men who are lacking gonadotropins, treatment with hCG causes external sexual maturation, and with the subsequent injection of hMG or follitropin, spermatogenesis occurs
- Multiple births can occur



Gonadotropins

- In females adverse effects include ovarian enlargement and possible hypovolemia
- Men may develop gynecomastia



Prolactin

- Secreted by the anterior pituitary
- Its secretion is inhibited by dopamine acting at D2 receptors
- Its primary function is to stimulate and maintain lactation
- Decreases sexual drive and reproductive function
- The hormone binds to a transmembrane receptor which activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation

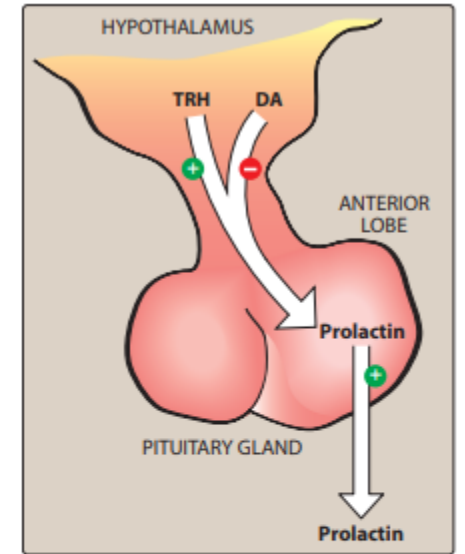


Figure 23.6
Secretion and action of prolactin. TRH = Thyrotropin-releasing hormone. From Preston RR, Wilson TE: Lippincott Illustrated Reviews: Physiology. Lippincott Williams and Wilkins (2013).



Prolactin

- There is no preparation available for hypoprolactinemic conditions
- Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is usually treated with D2-receptor agonists, such as bromocriptine and cabergoline
- Bromocriptine and cabergoline can be used for treatment of pituitary microadenomas, macroprolactinomas and hyperprolactinemia
- Adverse effects of bromocriptine and cabergoline:
 - Nausea, headache, and sometimes psychiatric problems

Hormones of the posterior pituitary

- Vasopressin and oxytocin
- Not regulated by releasing hormones
- Synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals:
 - High plasma osmolarity
 - Parturition

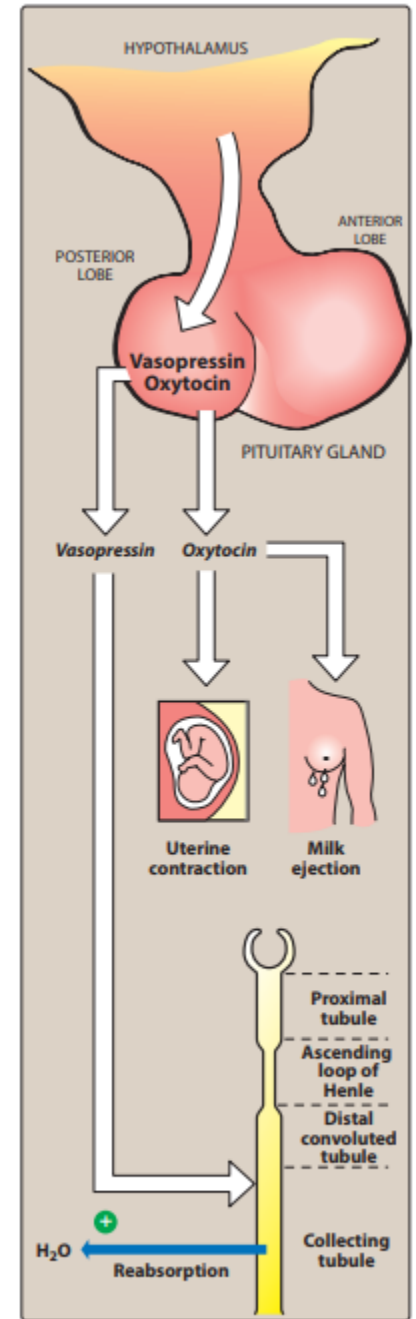


Figure 23.7
Actions of oxytocin and vasopressin.





Hormones of the posterior pituitary

- Vasopressin and oxytocin
- Each is a nonapeptide with a circular structure due to a disulfide bridge
- Reduction of the disulfide inactivates these hormones
- Given parenterally because they are susceptible to proteolytic cleavage



Oxytocin

- Used IV in obstetrics to stimulate uterine contraction to induce or reinforce labour
- The sensitivity of the uterus to oxytocin increases with the duration of pregnancy when it is under estrogenic dominance
- Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli
- Toxicities are uncommon when the drug is used properly
- Hypertension, uterine rupture, water retention, and fetal death have been reported



Oxytocin antagonist

- Oxytocin antagonist: Atosiban
- An inhibitor of the hormones oxytocin and vasopressin
- Used as an intravenous medication as a labor repressant (tocolytic) to halt premature labor



Vasopressin

- Antidiuretic hormone
- In the kidney it binds to the V2 receptor to increase water permeability and reabsorption in the collecting tubules
- Has antidiuretic and vasopressor effects
- Some effects of vasopressin are mediated by the V1 receptor, which is found in liver, vascular smooth muscle (causing constriction)



Vasopressin

- Therapeutic use:
 - Treatment of diabetes insipidus
 - Management of cardiac arrest and in controlling bleeding due to esophageal varices or colonic diverticula



Vasopressin

- Adverse effects:
 - Water intoxication
 - Hyponatremia
 - Headache
 - Bronchoconstriction
 - Tremor
- Caution must be used when treating patients with coronary artery disease, epilepsy, and asthma



Desmopressin

- Vasopressin analog
- Has minimal activity at the V1 receptor making it largely free of pressor effects
- Longer duration of action than vasopressin
- Used for diabetes insipidus and nocturnal enuresis
- Administered intranasally or orally
- Local irritation may occur with the nasal spray
- The nasal formulation is no longer indicated for enuresis due to reports of seizures in children using the nasal spray



Vasopressin antagonist

- Conivaptan (vasopressin receptor antagonist)
 - A non-peptide inhibitor of ADH, inhibits vasopressin receptor and used in SIADH
- Other drugs used in syndrome of inappropriate ADH (SIADH): Lithium, Demeclocycline
- Drugs used in the treatment of nephrogenic diabetes insipidus :
 - Thiazides, amiloride